and a very low plasma LH level; a pituitary tumour must be excluded by radiological investigation. Postpubertal disturbances of gonadotrophin secretion are common in young women and the usual type of secondary amenorrhoea is probably due to failure of the hypothalamus to produce gonadotrophin releasing factor. This usually corrects itself in a matter of months but if secondary amenorrhoea is prolonged a pituitary tumour must be excluded. Isolated deficiency of growth hormone does occur and should be looked for in all children below the third percentile in height.

REPLACEMENT THERAPY

The replacement therapy required in a patient with hypopituitarism, whether due to a pituitary tumour or some other cause, will depend on the trophic hormones that are deficient. For this reason detailed endocrine assessment is required and, as the situation may change, the hormone status must be reviewed regularly.

If there is evidence of ACTH deficiency, replacement therapy is most conveniently given with cortisone or prednisone. Aldosterone production by the adrenal cortex is little affected by loss of ACTH and therefore the glucocorticoid action of prednisone is adequate. The dose will be 3 to 6 mg per day given in divided doses eight-hourly (1 mg tablets of prednisone should be used). Patients on corticosteroid replacement therapy

for hypopituitarism must carry cards indicating that they need this treatment. If they get any fever or intercurrent illness or have to have surgical operations the dose will need to be increased. Vomiting of the tablets necessitates intramuscular injection. It should be noted that if the patient is deficient of ACTH all pituitary trophic hormones are likely to be lacking, but the reverse does not apply. If TSH deficiency is found replacement should be with thyroxine, 0.3 mg daily.

Gonadotrophin deficiency in premenopausal women may be corrected by injections of the appropriate gonadotrophin if pregnancy is desired—but otherwise cyclical therapy with oestrogen-progestogen mixtures may be used to maintain the normal condition of the breasts, uterus, and vagina. If this is not done the patients often complain of dryness of the vagina and dislike of intercourse. Gonadotrophin deficiency in young men who may want children should be corrected by injections of chorionic gonadotrophin with the hope that the addition later of a gonadotrophin with an FSH component will restore spermatogenesis. For older men fluoxymesterone by mouth or injections of long-acting testosterone will restore libido and potency but not fertility.

Children with growth-hormone deficiency who are short and whose epiphyses have not fused may benefit from injections of human growth hormone. It is therefore very important in children with hypopituitarism not to give gonadotrophin or sex-hormone replacement therapy until the maximum growth has been achieved.

Computers in Medicine

Computer Programme to Estimate Recurrence Risks for Multifactorial Familial Disease

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Summary

A computer programme to estimate recurrence risks for multifactorial genetic disease in affected families uses parameters on population prevalence and on heritability of liability of the condition and details of the family history. Information on affected and unaffected relatives (first-degree, second-degree, and third-degree) and on sex or age effects on prevalence and on heritability can all be accommodated by the programme.

Introduction

Many common familial diseases are not inherited in a simple Mendelian manner but may be the result of many genetic and environmental factors, so-called multifactorial inheritance. The recurrence risks for such diseases are not the simple Mendelian ratios and the best available estimates are the empiric risks—the observed frequency of the disease in relatives of affected

patients. In practice, however, these risks may vary with the sex, severity, and age of onset in affected individuals and with the number of affected members in the family concerned. New methods of estimating recurrence risks for multifactorial conditions have been developed,^{1,2} and these can be used in genetic counselling to supplement empiric risks in complex situations. The objects of this paper are to describe a computer programme available for calculating recurrence risks and to demonstrate its use in genetic counselling problems.

Scope

A wide range of possible situations can be covered by the programme. It can accommodate: (1) affected and unaffected relatives; (2) any family history, giving (a) accurate risks within sibships but (b) approximate risks with second-degree and third-degree relatives; (3) differences in prevalence and heritability for different sexes or different severity or age classes for the disease; and (4) risks to future children or risks to an individual conditional on his not being affected so far.

A further development of the programme may allow the use of information on continuous variables associated with a disease (such as blood glucose levels in diabetes or personality scores in schizophrenia) and so improve the accuracy of the risk estimate in a given family.

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Requirements

The most important requirements in genetic counselling are an accurate diagnosis of the condition involved and a complete family history for the condition. To estimate recurrence risks for multifactorial familial disease the population prevalence of the condition and the heritability of liability³ to the condition are also required. The heritability of liability is measured from the frequency of the condition in relatives of affected individuals. Any effects of sex, severity, or age on the frequency of the condition must be taken into account in measuring the heritability and estimating the recurrence risks.

Computer Programme

A computer programme, RISKMF (the programme is written in FORTRAN and is available from the department of human genetics, Western General Hospital, Edinburgh), can be used to estimate the recurrence risks. Full details of the multifactorial model and of the methods used in the programme for calculating the recurrence risks were given by Smith.¹ The

FIG. 1—Codes used for relatives (see text).

FIG. 2—Coded family history for family with cleft lip (with or without cleft palate). (Square=male. Circle=female. Black symbol=affected subject. See text for code.)

computer input to the programme consists of four items: (1) identification details—for example, family name, date, disease name; (2) the number (NCLASS) of severity or age (SA) classes specified; (3) the prevalence (P) and heritability (H) parameters for the condition; and (4) a coded family history (see below). These input details are printed in tables by the computer for checking and for reference. The recurrence risks are then calculated and printed.

Coded Family History

A simplified form of the family pedigree is used, coded as shown in Fig. 1. The father is coded 1, and 5 and 6 code paternal second-degree and third-degree relatives respectively (and similarly for 2, 7, and 8 on the maternal side). Siblings are coded as 3 and siblings' children as 4. If the individual whose risk is sought is already born a code 9 is used. The form of the input details for each coded group in the pedigree is shown in the following examples.

INPUT DETAILS

- (1) DISEASE CONDITION, FAMILY IDENTIFICATION, DATE, ETC. FORMAT (80A1)
FAMILY 0001 CLEFT LIP (WITH OR WITHOUT CLEFT PALATE) AUGUST 1971
(2) NUMBER OF SEVERITY-AGE (SA) CLASSES SPECIFIED FORMAT (12)
1=NCLASS
(3) PARAMETER MATRIX, PREVALENCE (P), HERITABILITY (H) FORMAT (6F6.4)

BOTH SEXES		MALES		FEMALES		SA-CLASS 1 FORMAT (511)
P	H	P	H	P	H	
0.0010	0.7500	0.0013	0.7500	0.0007	0.7500	
CODE	NO.	SEX	CLASS	STATUS		
1	1	1	1	0		
2	1	2	1	1		
3	2	1	1	0		
3	1	1	1	1		
3	1	2	1	1		

OUTPUT DETAILS

RECURRENT RISKS BY SEVERITY-AGE CLASS AND SEX			
SEVERITY	AGE CLASS	BOTH SEXES	MALE FEMALE
1		0.134	0.155 0.109

FIG. 3—Input details and recurrence risks for the family (Fig. 2) with cleft lip (with or without cleft palate).

EXAMPLE 1

Consider the family in Fig. 2 with cleft lip (with or without cleft palate). The numbers refer to the codes in the simplified pedigree. The population prevalence of the condition is about 0.1% (0.13% in males and 0.07% in females) and the heritability is estimated as about 75% in both sexes.⁴ The input details are listed in the sample of computer output in Fig. 3. The recurrence risks to future children in the sibship are then calculated and printed. The estimated risk in this family is 13.4%—15.5% for males and 10.9% for females.

FIG. 4—Coded family history for family with diabetes mellitus. Key as for Fig. 2. Oblique line through symbol indicates subject dead. Superior number against white symbol indicates current age or age at death. Superior number against black symbol indicates age at onset. Inferior numbers refer to pedigree codes.

EXAMPLE 2

As a more complex example consider a family with diabetes mellitus. For diabetes there are sex effects on prevalence and age effects on heritability. Early-onset and late-onset cases are taken to belong to the same genetic condition.⁵ In the family history given in Fig. 4 the age shown is the age at onset if the person is diabetic and the current age if the person is not diabetic. The pedigree codes are inserted as before. What is the risk of diabetes to future children at different stages in their lives?

The input details are given in the computer output, as shown in Fig. 5. Four severity-age classes have been specified corresponding to four onset-age classes (0-19 years, 20-39 years, 40-59 years, and 60-79 years), so NCLASS=4. The varying prevalence and heritability parameters for different onset-age and sex classes, derived from Smith *et al.*,⁵ are also shown. The severity-age class coded is the onset-age class if the relative is affected and the current-age class if the relative is not affected. The risks of diabetes to future children throughout their lives is given by the computer, as in Fig. 5. Similarly, for a person

INPUT DETAILS

- (1) DISEASE CONDITION, FAMILY IDENTIFICATION, DATE, ETC.
FAMILY 0823 DIABETES MELLITUS
(2) NUMBER OF SEVERITY-AGE (SA) CLASSES SPECIFIED
4 = NCLASS
(3) PARAMETER MATRIX, PREVALENCE (P), HERITABILITY (H)

BOTH SEXES		MALES		FEMALES		SA-CLASS
P	H	P	H	P	H	
0.0005	0.7100	0.0005	0.7100	0.0004	0.7100	1
0.0019	0.6000	0.0021	0.6000	0.0016	0.6000	2
0.0075	0.5800	0.0079	0.5800	0.0071	0.5800	3
0.0192	0.5300	0.0192	0.5300	0.0192	0.5300	4

(4) INFORMATION MATRIX ON RELATIVES

CODE	NO.	SEX	CLASS	STATUS
1	1	1	1	1
2	1	2	3	0
3	1	2	2	0
3	1	2	1	1
4	1	2	1	0
5	2	1	4	0
5	1	2	4	0
5	1	1	3	0
6	1	1	2	0
6	1	2	1	0
7	1	1	4	0
7	1	2	3	1
7	1	2	3	0
7	1	1	3	0
8	1	2	2	0
8	1	1	2	1

OUTPUT DETAILS

RECURRENT RISK BY SEVERITY-AGE CLASS AND SEX			
SEVERITY-AGE CLASS	BOTH SEXES	MALE	FEMALE
1	0.097	0.097	0.085
2	0.153	0.161	0.140
3	0.293	0.300	0.287
4	0.406	0.406	0.406

FIG. 5—Input details and recurrence risks for the family (Fig. 4) with diabetes mellitus.

who is not affected so far the risk of contracting diabetes can be estimated by the programme.

Discussion

This brief account should illustrate the scope of the RISKMF programme in evaluating recurrence risks for multifactorial conditions. In addition to estimating risks for individual families the programme can be used to provide theoretical recurrence risks in general situations or for comparisons with observed risks. For example, risks to children if both parents are affected (so-called dual matings), risks for sporadic cases, risks with two, three, or more affected children, and so on, can all be studied by the programme. The maximum risk with multifactorial inheritance, assuming a heritability close to 100%, can also be derived. Similarly the effects of varying the prevalence and heritability parameters or the number of SA classes or of including unaffected relatives or second-degree and third-degree relatives can all be studied empirically through the programme.

The programme can handle several families in sequence with the same or different diseases. At present data are fed to the computer by means of punch cards, but an interactive system with direct access to the computer by a teletype or other remote terminal is planned. Computing time per family is usually less than 30 seconds (I.B.M. 360/50). The programme, with documentation, is available on request from this department. Alternatively family histories, with the relevant prevalence and heritability parameters, may be submitted to the department for estimation of risk. Morton⁶ has also developed a computer programme (COUNSEL) for estimating recurrence risks. His programme will allow the user to estimate risks by using several genetic models, including the multifactorial model.

The programme might also be used to prepare user tables of recurrence risks for a variety of family histories for a given condition, such as the specialty of a department, or for a particular geographical area. For example, the recurrence risks for spina bifida or anencephaly or both in a high-incidence area have been estimated for different numbers of affected relatives by using the data of Carter *et al.*⁷ from South Wales (combined incidence 0.78%, heritability 64%). These are given in the Table and show how the risk increases as further affected relatives, including second-degree and third-degree relatives, are added. If there is no previous family history, however, the estimated risk is lower than the empiric risk.

Estimated Recurrence Risks for Spina Bifida or Anencephaly or Both

Family History	Estimated Risk (%)
One sib affected	5.5
Parent and sib affected	13.0
Two sibs affected	20.6
Three sibs affected	9.2
One sib and a second-degree relative affected	7.3
One sib and a third-degree relative affected	3.7
One sib affected, no other family history	

The use of these methods to estimate recurrence risks in practice may be queried on several grounds. In man it is always difficult to separate genetic and non-genetic effects, and these may be confounded in estimating heritability. This is less serious for risk estimation, however, since non-genetic effects may also be involved in risks to relatives. The multifactorial model is used to describe the observed frequencies of a condition in relatives, but the true mode of inheritance is usually not known. This may not be too critical in evaluating risks, for it has been shown⁸ that the risks are similar for different modes of inheritance—unless strict Mendelian inheritance is involved. Another difficulty in practice may be the lack of adequate estimates of population prevalence and of heritability, but these should accrue in time.

Finally, the recurrence risks for multifactorial conditions are usually not high unless the disease is common or there are several affected relatives in the family. Thus the methods described here may be of most value (1) in common familial conditions or (2) if there are complicating sex or age effects or (3) if there is a complex family history or (4) if there are poor empiric estimates of risk. Moreover, they provide a standard system and a rationale for estimating recurrence risks where none have been available previously. Thus they may help to provide better information for genetic counselling, for the identification of high-risk groups, for the indication for antenatal diagnosis, and in general for the prevention and treatment of familial disease.

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